REMARKS

FORMAL MATTERS:

Claims 1, 2, 4, 6, 8-11, 15 and 19-33 are pending after entry of the amendments set forth herein, claims 3, 5, 7, 12-14 and 16-18 having been cancelled previously.

Claims 8, 27 and 29 are amended herein. Support for the amendments is found in the claims as originally filed and throughout the specification.

With respect to claims 8, 27 and 29, support for oral administration of the iSe compound is found, e.g., at paragraphs [0054], [0058], [0062] and elsewhere.

No new matter is added.

REJECTIONS UNDER §103(A)

Claims 1, 2, 4, 6, 8-11, 15 and 19-33 were rejected under 35 U.S.C. 103(a) as allegedly unpatentable over U.S. Patent No. 6,656,509 to Stiefel et al. (hereinafter "Stiefel") in view of Applicants' "admission", U.S. Patent No. 4,665,897 to Lemelson et al. (hereinafter "Lemelson"), U.S. Patent No. 6,511,971 to Gorun et al. (hereinafter "Gorun"), Hehr et al. (Med. Klin. (1997) 92(3): 48-49, Abstract and Abdullayev et al. (Selen. Biol., Mater. Nauchn. Konf. (1974), pp. 126-8) (hereinafter "Abdullayev"). Applicants respectfully traverse for the reasons set forth below.

According to the post-*KSR* Patent Office promulgated examination guidelines on determination of obviousness, when office personnel reject claims by attempting to combine prior art elements according to allegedly known methods to yield predictable results, the Office must resolve the Graham factual inquiries and articulate:

(1) "a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;"

(2) "a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately; and"

(3) "a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable." (Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices at 57529, *citing KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q. 2d 1385, 1395 (U.S. 2007)).

Thus, the rationale to support a conclusion that a claim would have been obvious is that "all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions," and that "the combination would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of the invention." *Id.*

The cited combination of Stiefel, Lemelson, Gorun, Hehr and Abdullayev fails to render the claims obvious, at least because the combination of references does not teach or suggest each and every element of the claims. For example, the cited combination fails to teach or suggest the administration of radiation therapy within 6 hours after administering an inorganic selenium-containing compound (hereinafter an "iSe compound").

Stiefel, the primary reference relied upon in the Action, does not remotely teach or suggest the *sequential* administration of an iSe compound followed by *radiation* therapy. First, Stiefel teaches that "chemotherapy is considered the so far [sic] most efficient therapeutic method" (see Stiefel at column 4, lines 37-38, emphasis added) and that "[i]t is therefore the object of the present invention to provide a possibility of enhancing the effect of antitumor drugs and to provide said drugs in a suitable form of administration." See Stiefel at column 4, lines 47-50 (emphasis added). As such, one of ordinary skill in the art – upon reviewing Stiefel – would not contemplate administering a combination of an iSe compound with radiation therapy. Applicants note that if a proposed modification would render a prior art invention unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the modification. See MPEP §2143.01(V), citing *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Accordingly, there was no suggestion or motivation to modify Stiefel, e.g., by replacing cytostatic drugs with radiation therapy, when Stiefel touts the therapeutic efficiency of antitumor drugs and expressly states that the object of the invention is to enhance the effect of such antitumor drugs. Applicants also note that Stiefel relates, at most, to administration of a selenium-containing compound with a cytostatic agent, i.e., an agent that *inhibits* tumor cell

growth but does not itself *kill* tumor cells (unlike radiation therapy as recited in the independent claims). Applicants note that inorganic selenium compounds are generally cytotoxic, and one of skill in the art would not think to use the inorganic selenium-containing compounds of the claimed invention with the cytostatics of Stiefel. Indeed, Stiefel teaches that organic selenium compounds are preferred: "[t]he use of organic selenium compounds is to reduce toxicity in comparison with inorganic selenium compounds…." See Stiefel at col. 4 line 67 – col. 5 line 4.

Regarding the purported synergistic effect disclosed by Stiefel, Applicants point out that such an effect was only observed *in vitro*, and that Stiefel unambiguously (and importantly) teaches that a synergistic effect occurs only when the cytostatic agent and the selenium compound are administered simultaneously. See, e.g., Stiefel at column 4, lines 61-65 (stating that "[t]he following examples will demonstrate that *in vitro* a simultaneous treatment with the above-mentioned components surprisingly yields a distinct synergistic, i.e. superadditive, antitumor effect") (emphasis added).

Moreover, Stiefel teaches that a synergistic effect is only observed at doses of chemotherapeutic drugs that one of skill would doubt to be clinically relevant:

> When the pancreatic tumor xenograft PAXF 736 was treated simultaneously with sodium selenite and mitomycin C or gemcitabine, no synergistic effect could be detected, neither at a concentration of 3 μM nor at a concentration of 30 μM sodium selenite. Also no synergism was observed between 3 μM sodium selenite and all of the tested concentrations of chemotherapeutic agents in the xenograft PAXF 546 or when low concentrations of the chemotherapeutic agents were combined with 30 μM of sodium selenite. In contrast, when higher doses of chemotherapeutic drugs at which cytotoxic effects could be observed were combined with 30 μM sodium selenite, synergism was observed in combination with mitomycin C and gemcitabine (Tables 4a, 4b). See Stiefel at column 16 line 64 – column 18 line 4.

As such, Stiefel teaches that the utility of administering a selenium compound is only realized when the compound is administered *simultaneously* with a *cyctostatic chemotherapeutic drug* provided at *high concentrations*. In stark contrast to the teachings of Stiefel, the inventors of the present invention have discovered that an initial administration of an iSe compound has the unexpected effect of markedly *sensitizing* a tumor to *subsequent radiotherapy*. See, e.g., the

declaration of inventor Susan Knox dated October 7, 2009. Also surprising was that "pretreatment" with an iSe compound neither sensitized normal intestinal crypt cells nor exhibited significant toxicity. *Id.* For these and other reasons, the disclosure of Stiefel bears little resemblance to the claimed invention.

Neither Lemelson nor Gorun make up for the deficiencies of Stiefel. The Action cites Lemelson as disclosing the "use of radiation therapy using neutron beams to active nuclide species at the site of the tumor" and Gorun as disclosing that "photodynamic sensitizers which produce singlet molecular oxygen are used to destroy cancerous tissue." See Action at p. 4. The relevance of the Lemelson and Gorun references to the claimed invention is not readily apparent, especially because the Action does not specify to which claims (or limitations therein) the references are being applied. Applicants respectfully note that "[t]he pertinence of each reference, if not apparent, must be clearly explained and each rejected claim specified." See MPEP §706(c)(2).

The Action cites Heir for disclosing "administration of 400 micrograms of sodium selenite after every course of irradiation of the rectal tumor region and lymph nodes (Abstract)." See Action at p. 3, third paragraph. The most pertinent aspect of the disclosure of Heir as it relates to the present invention is that the selenite is administered *after* irradiation. This makes sense, because Heir is only concerned with the potential for selenite treatment to *mitigate the side-effects of radiotherapy* (e.g., see Heir at p. 6), as opposed to having a *radiosensitizing* effect on the tumor. It follows that Heir fails to teach or suggest administering radiation therapy to a subject within 6 hours after administering an iSe compound, and therefore fails to remedy the deficiencies of Stiefel, Lemelson and Gorun.

The Action cites Abdullayev for disclosing that "sodium selenite given parenterally to mice and rats with sarcoma M-1, Guerin carcinoma, Walker carcinoma, lymphosarcoma and Ehrlich ascites tumors inhibited tumor growth and that antineoplastic activity was enhanced when sodium selenite treatment was combined with radiation." See Action at p. 3, 5th paragraph. Applicants have obtained an English translation of the complete disclosure of Abdullayev, which translation accompanies the Information Disclosure Statement provided herewith. As was the case with Stiefel and Heir, Abdullayev fails to teach administration of an iSe compound prior to administration of radiation therapy, let alone administering the radiation

therapy within 6 hours after administering the iSe compound. As such, Abdullayev does not make up the deficiencies of Stiefel, Lemelson, Gorun and Heir, and the cited combination fails to render the claims obvious.

Regarding the feature of each of the independent claims that the radiation therapy is administered within 6 hours after administration of the iSe compound, the Action alleges that "it would be readily apparent to one of ordinary skill in the art that administration of inorganic selenium can occur prior to, concurrently or after administration of radiation therapy. As such, it is well within the skill of one of ordinary skill in the art to administer radiation therapy after administering the inorganic selenium compound at various time intervals… including within a six hour time period." See Action at pp. 5-6. Applicants respectfully disagree, at least because the references available to one of skill in the art (e.g. Stiefel and Heir) – *prior to Applicants' disclosure* – teach administering a selenium compound either simultaneously or after, but not before, a primary therapeutic modality. As such, there was no teaching or suggestion in the art to administer an iSe compound and radiation therapy in the sequence (or within the time-frame) as set forth in the claimed invention.

At least for the reasons set forth above, the combination of Stiefel, Lemelson, Gorun, Heir and Abdullayev fails to teach or suggest each element of the independent claims. As such, the cited combination fails to render the claimed invention obvious, and Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is respectfully requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-333.

Respectfully submitted,

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Enclosures:

- Information Disclosure Statement

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